Performance fatigability is not regulated to a peripheral critical threshold

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Short title: Fatigability is task-dependent

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No funding was received for the work. The authors have no conflicts of interest to declare.

ABSTRACT

The *critical threshold hypothesis* proposes that performance fatigability during high-intensity exercise is tightly regulated by negative-feedback signals from the active muscles. We propose that performance fatigability is simply dependent on the exercise mode and intensity; the consequent adjustments, in skeletal muscle and the other physiological systems that support exercise, interact to modulate fatigue and determine exercise tolerance.

KEY WORDS

Afferent feedback; cardiovascular; exercise; fatigue; fatigability; muscle; respiratory

SUMMARY

The magnitude of performance fatigability observed after high-intensity exercise is task-dependent, and not regulated to a peripheral critical threshold.

KEY POINTS

- Fatigue is a symptom, or percept, that limits exercise performance in healthy individuals.
- The *critical threshold hypothesis* emphasizes a critical role for metabolite-mediated afferent discharge in determining exercise tolerance. Specifically, negative-feedback signals from active muscle act to restrain central motor command to limit metabolic perturbation within locomotor muscle, and therefore constrain decrements in the quadriceps potentiated twitch force (a measure of performance fatigability) to a specific, task-dependent level.

- We propose that performance fatigability is simply determined by the mode and intensity of the task; these factors dictate the active muscle mass, and demand on other physiological systems. The consequent adjustments interact to modulate fatigue, which determines exercise tolerance.
- We review existing correlative and experimental evidence to demonstrate that performance fatigability of skeletal muscle is but one limiting factor in modulating fatigue and exercise tolerance, the importance of which varies with the exercise task.

INTRODUCTION

The study of fatigue and the factors that limit, or regulate, exercise performance has captivated scientists for centuries, but a thorough explanation of the etiology of this condition remains elusive (1, 2). The classic writings of Angelo Mosso (3) identified the two phenomena that characterize fatigue; i) a physical component represented by a diminution of muscular force, and ii) fatigue as a sensation. Over a century later, debate still ensues over our understanding of fatigue, and specifically the sensation of fatigue. Mosso's original description of fatigue was based on the concept of repetitive contractions that induced neuromuscular adjustments in healthy populations that were reversible by rest.. This idea of an organic cause for a perceptual construct remains pertinent for our conceptualization of fatigue in the exercise sciences (4). For the purpose of this review fatigue will be discussed within the taxonomy proposed by Enoka & Duchateau (2). Specifically, fatigue is defined as a symptom or percept, characterized by feelings of tiredness and weakness, in which physical and cognitive function are limited by interactions between performance fatigability and perceived fatigability (2). Performance fatigability refers to the decline in an objective measure of performance; such as the production of maximal voluntary force, the ability to provide an adequate signal to voluntary activate muscle, or the involuntary twitch response to stimulation (2). Throughout this review, we will use the reduction in the involuntary twitch force in response to motor nerve stimulation as our indicator of performance fatigability. Perceived fatigability refers to the sensations that regulate the integrity of the performer; these sensations can be modulated by disruptions to homeostasis (e.g. core temperature, hydration status, substrate availability) and modifications in psychological state (e.g. arousal, motivation, mood) that contribute to the perception of effort required for the task (2). Performance and perceived

fatigability are interdependent, and interact to modulate and determine the symptoms of fatigue. In healthy participants, the physiological adjustments associated with high intensity exercise are strongly associated with perceived fatigability and changes in the rating of perceived exertion (RPE), such that there is a tolerable degree of fatigue the person performing the exercise is willing to experience at any given point during an exercise task. Such a definition is similar to the idea of a sensory tolerance limit (5, 6), but emphasizes the myriad of modulating factors, both physical and psychological, that could contribute to the symptom of fatigue the exerciser is willing to endure at any given point during an exercise challenge.

The *critical threshold hypothesis* proposes a pivotal role for metabolite-mediated afferent discharge in regulating 'central motor command' (defined as the activity of premotor and motor areas of the brain related to voluntary muscle action; 7) during exercise, and thus exercise performance. This hypothesis proposes that adjustments in contractile function are constrained during high-intensity exercise in healthy participants by negative-feedback signals from active muscles. Specifically, exercise-induced alterations of the intramuscular metabolic milieu are proposed to provoke inhibitory input from group III and IV afferents that act to restrain central motor command in order to protect against excessive disruption to muscle homeostasis (8). This hypothesis has been experimentally tested via studying the decline in the electrically or magnetically evoked twitch response to motor nerve stimulation as an indicator of fatigue-related changes in the muscle. A number of studies (e.g. 8, 9, 10-17) have observed an unvarying post-exercise reduction in the involuntary quadriceps potentiated twitch amplitude ($Q_{tw,pot}$, often defined as peripheral fatigue, or locomotor muscle fatigue, but hereafter referred to as performance fatigability) to a range of

111 exercise tasks and experimental interventions, and provided interpretations in support
112 of this concept.
113
114 Recently, the authors of the critical threshold hypothesis revisited the sensory
115 tolerance limit concept proposed by Gandevia (6) to offer a more holistic explanation
116 for understanding the limits to exercise tolerance (5). The sensory tolerance limit
117 concept proposes it is the sum of all neural feedback, feedforward signals, and
118 associated sensations that interact to limit exercise performance. Such an idea is
119 qualitatively similar to the taxonomy proposed by Enoka & Duchateau (2) discussed
120 previously. This notwithstanding, the idea that group III/IV afferent feedback acts to
121 reduce central motor command and the subsequent development of performance
122 fatigability to a specific level remains a key feature of these updated proposals, but
123 with an acknowledgement that the magnitude of adjustments varies between
124 individuals and the exercise task (5).
125
126 The aim of this review is to propose that performance fatigability is not constrained to
127 a task-specific, critical peripheral threshold, but rather simply depends on the muscle
128 mass engaged during the task, and the associated disruption to homeostasis in
129 multiple physiological systems. The muscle mass recruited during exercise is
130 dependent on the intensity and mode of the task; these two critical factors will dictate
131 the magnitude of performance fatigability. Specifically, we propose that for the same
132 mode of exercise, reductions in $Q_{tw,pot}$ will increase with exercise intensity, primarily
133 because a greater proportion of the active musculature will be activated and exhausted
134 as the force requirements of the task increase. Furthermore, we propose the
135 adjustments as the active muscle mass increases during different exercise modes (e.g.

single limb < double limb < whole body locomotor) are progressively dictated by the demand placed on maintaining the homeostasis of other competing physiological systems that support exercise (e.g. cardiovascular, respiratory). As a consequence, the magnitude of performance fatigability is lower as other adjustments contribute to the maximum tolerable symptom of fatigue the exerciser is willing to endure. We propose the observation of a consistent magnitude of end-exercise performance fatigability is due to the characteristics of the task, and not a result of regulation to a critical threshold. Disruption to the metabolic milleu of the muscle tissue is but one potential modifier of fatigue, and varies in importance depending on the exercise task. This notwithstanding, the ability of skeletal muscle to meet the demands of exercise is likely to be the primary modulator of fatigue and thus exercise performance, as skeletal muscle will incur greater metabolic stress relative to it's maximum capacity in comparison to the cardiac and respiratory muscle systems that support exercise (18). This elegant design feature of the human body ensures that the homeostatic physiological systems responsible for supporting life, do not approach exhaustion during, and continue maintaining homeostatic functions after, exhaustive exercise (18). However, while skeletal muscle will typically be the primary limiter of exercise, the increased demand on cardiac and respiratory muscle systems, particularly at the point of task failure, will still contribute to modulating the symptom of fatigue. Ultimately, we propose it is the percept of fatigue that is regulated during exercise, underpinned by changes in the factors that modulate performance and perceived fatigability, which will vary in their importance depending on the exercise task. These ideas are explicated in this review, alongside a reinterpretation of the correlative and experimental evidence that seemingly supports the critical threshold hypothesis.

161

162 **Performance fatigability and active muscle mass**

163 For the same relative intensity, we propose the magnitude of active muscle mass
164 required for the exercise task will modulate the degree of performance fatigability,
165 because of the consequent challenge to whole-body homeostasis that will contribute
166 to the tolerable magnitude of fatigue. Data from comparisons between modes of
167 exercise within (13, 14), and between studies (9, 19-21) support this idea.

168

169 Rossman *et al*. (13, 14) directly investigated the effect of varying the active muscle
170 mass on the magnitude of end-exercise performance fatigability. In the first of these
171 studies (14), participants voluntarily exercised to the limit of tolerance at 85% of
172 modality-specific maximal intensity in two exercise modes; isoinertial knee
173 extension, and locomotor cycling exercise. The magnitude of performance fatigability
174 was higher after knee extensor exercise when the active muscle mass was small,
175 compared to cycling exercise when the active muscle mass was larger (−53 ± 2 vs.
176 −34 ± 2% reduction in $Q_{tw,pot}$, respectively). The same authors subsequently
177 confirmed these observations studying single-leg knee extension exercise compared to
178 double-leg knee extension exercise, thereby circumventing the potential confounding
179 factor of mode-specific exercise responses (13). Specifically, participants completed
180 single-leg and double-leg knee extension exercise to their self-determined limit of
181 tolerance at the same relative modality-specific exercise intensity. The magnitude of
182 performance fatigability was higher after single leg knee extension exercise (−44 ±
183 6%) compared to double-leg knee extension exercise (−33 ± 7%). In both studies the
184 higher active muscle mass was also concurrent with higher cardiorespiratory
185 responses (13, 14), and in the second of these studies, the increase in the *vastus*

186 *lateralis* integrated electromyogram signal (iEMG) from the first to the last minute of
187 exercise, was higher during single-leg compared to double-leg exercise (147 ± 24 vs.
188 85 ± 15%) indicative of a progressively greater recruitment of additional muscle mass
189 during the single-leg trial. These data demonstrate that when the active muscle mass
190 is smaller, a greater proportion of the available musculature is engaged during the
191 task, and the demand on other physiological systems is lower. In concert, these factors
192 lead to a greater post-exercise reduction in $Q_{tw,pot}$, as the exerciser can tolerate greater
193 local muscular stress before the perception of effort becomes excessive.
194
195 Further comparisons between exercise modes also illustrates how the active muscle
196 mass modulates performance fatigability. For high intensity cycling exercise (80-90%
197 of peak intensity measured during an incremental test to the limit of tolerance, usually
198 abbreviated as P_{max}) numerous research groups, including our own, have shown a
199 relatively consistent post-exercise reduction in potentiated twitch force of
200 approximately 35% (8, 9, 19, 20, 22). When the task requires a smaller active muscle
201 mass, the absolute reduction in twitch force after exhaustive exercise is higher. For
202 example, we observed a reduction in $Q_{tw,pot}$ of 60 ± 13% after 3 × 30 s MVCs (23),
203 and as previously demonstrated Rossman *et al*. (13, 14) reported absolute reductions
204 in $Q_{tw,pot}$ of 44% and 53% after single limb knee extension exercise. Conversely,
205 during running exercise, when the active skeletal muscle mass is increased, the
206 absolute decline in potentiated twitch is lower; even for maximal repeated sprint
207 exercise (−24 ± 9%; 21). Finally, prior high-intensity arm cycling reduces exercise
208 tolerance during leg cycling, and the worsened leg cycling exercise performance is
209 associated with a lower reduction in $Q_{tw,pot}$ (−38 ± 13% vs. −26 ± 10%; 19). This last
210 finding underlines the effect that engaging a higher active muscle mass has on

211 modulating fatigue. Even though the upper limbs do not directly contribute to cycling
212 exercise, the higher sensory input from engaging and exhausting a greater volume of
213 skeletal muscle was proposed to limit subsequent cycling performance and constrain
214 performance of the locomotor muscles because the maximum tolerable degree of
215 fatigue the exerciser was willing to endure was reached more rapidly (19). Figure 1
216 provides a simplified summary of our proposal that the active muscle mass modulates
217 the maximum tolerable symptom of fatigue, and the magnitude of performance
218 fatigability. Specifically, as the active muscle mass increases, the degree of
219 performance fatigability is lower as the sensory input from a larger muscle mass and
220 greater disruption to homeostasis in other physiological systems (e.g cardiovascular,
221 respiratory) increases; ultimately these adjustments summate to collectively modulate
222 the symptom of fatigue the exerciser experiences
223
224 Rossman *et al*. (13, 14) acknowledged the task-specificity of performance fatigability,
225 and proposed that a reduction in the exercising muscle mass permits the development
226 of greater performance fatigability because of a reduction in the source of group
227 III/IV afferent feedback to a more local, and less diffuse, signal. Central to this
228 interpretation remains the idea that feedback from group III/IV afferents act to inhibit
229 central motor command to skeletal muscle to restrict the development of performance
230 fatigability to a specific critical level. While conceptually similar, we propose that the
231 higher magnitude of performance fatigability observed after single compared to
232 double leg exercise is not tightly regulated to a task-specific level, but rather is simply
233 a consequence of a greater recruitment and subsequent stress of a greater volume of
234 skeletal muscle. The smaller active muscle mass (both involved and non-involved
235 skeletal muscle), and lower activation of cardiac and respiratory muscle systems

affords a greater mass-specific blood flow to the exercising muscle (24), and a progressively greater recruitment of additional muscle fibers (17). This smaller active muscle mass permits the exerciser to endure greater perturbations to contractile function as the threat to homeostasis is predominantly restricted to a single muscle group, and as such a larger magnitude of performance fatigability can be incurred before the fatigue elicited by the task is perceived as intolerable. As previously described, it is the symptom of fatigue that is the likely "regulated" variable determining exercise tolerance, modulated by interactions between the factors that underpin performance and perceived fatigability.

Performance fatigability and exercise intensity

The active muscle mass engaged during exercise interacts with exercise intensity (and consequent duration) to determine the magnitude of performance fatigability. Before any discussion of the importance of exercise intensity in determining performance fatigability, consideration of the well-established intensity-duration relationship characteristic of exercise performance is necessary. Briefly, the peak intensity of any mode of activity declines as the duration of the task increases. The relationship between intensity and duration can be described by a hyperbolic function with two key features; i) the intensity asymptote of the intensity-time hyperbola corresponds to a maximum sustainable intensity (the critical intensity, CI) and ii) the curvature constant of the hyperbola denotes a finite amount of work that can be performed above CI, termed *W'* (25). The CI denotes the boundary between the "heavy" and "severe" exercise intensity domains. Sustained activity above CI, in the severe domain, elicits perturbations to intramuscular homeostasis that ultimately result in task failure. Exercise below CI is theoretically fatigue-free, though in reality this

prediction is not correct (26). The performance and physiological characteristics of the intensity-duration relationship are critical to consider when discussing any integrated model of fatigue. For the most part, we will discuss data from exercise tasks completed to the limit of tolerance at intensities above the CI.

Within the same exercise mode, the intensity of the task can modulate the level of performance fatigability such that increases in intensity result in greater reductions in $Q_{tw,pot}$ (20, 22). However, the effect of intensity on performance fatigability is negligible when the active muscle mass is small, the intensity is above CI, and the relative demand on other modulators of fatigue is minimized (17). When the active muscle mass is higher, (such as during whole body locomotor exercise), the exercise intensity will influence performance fatigability; higher exercise intensities result in a greater recruitment and subsequent adjustment of the active musculature, and a greater reduction in potentiated twitch. These proposals are explained below.

During locomotor exercise (cycling and running) to volitional exhaustion, the degree of performance fatigability is modulated by exercise intensity. Specifically, data from our laboratory showed the reduction in $Q_{tw,pot}$ is exacerbated with increased exercise intensity (20, 22). For example, during constant-load cycling at relative intensities of 100%, 76% and 64% of P_{max}, we observed physiological responses consistent with exercise above CI in the severe domain, and post-exercise reductions in potentiated twitch force of −33%, −16% and −11%, respectively (20). Additionally, the greatest reductions (>50%) observed in potentiated twitch after cycling exercise have been reported after repeated sprint cycling exercise, which theoretically offers a model where exercise intensity is “all-out” or maximal (15, 16). The same pattern has also

286 been observed in running exercise; reductions in potentiated twitch after repeated
287 sprint running (−24%; 21) are higher than after 90 min of intermittent exercise
288 (−14%; 27), and after marathon running, where no significant decline in $Q_{tw,pot}$ has
289 been observed (28). In all of these studies there was a short time delay (typically 1-2
290 min) between the cessation of exercise and the measurement of performance
291 fatigability that could potentially confound comparisons both within- and between-
292 studies (29). However, even with this confound, the magnitude of difference observed
293 both between- and within-studies supports the supposition that locomotor exercise-
294 induced performance fatigability (measured by reductions in $Q_{tw,pot}$) is exacerbated
295 with increasing exercise intensity.
296
297 In contrast to whole body cycling exercise, the magnitude of performance fatigability
298 after exhaustive single limb exercise above CI is unvarying (17). Additionally,
299 magnetic resonance spectroscopy studies show a similar post-exercise metabolic
300 derangement after exhaustive single-limb exercise at different intensities above CI
301 (30), although these metabolic responses have previously been dissociated from
302 measurements of performance fatigability (31). Whilst these observations contradict
303 the proposal that exercise intensity can modulate the degree of performance
304 fatigability, they can be explained by the interactive effect of exercising with a small
305 active muscle mass. Specifically, when the active muscle mass is smaller there is a
306 lower demand on maintaining homeostasis in other physiological systems. As such,
307 the exerciser is able to tolerate a higher magnitude of performance fatigability specific
308 to reductions in contractile function before the maximum tolerable symptom of
309 fatigue is attained. The reader is referred back to Figure 1 for a graphical illustration
310 of this concept; during single-limb exercise the stress to other modulating factors is

311 minimized, such that a greater (perhaps maximum volitional) magnitude of
312 performance fatigability can be attained before the symptom of fatigue becomes
313 intolerable. This premise explains why exercise intensity modulates performance
314 fatigability after exhaustive exercise above CI in locomotor, but not single-limb
315 exercise modes.
316
317 **Challenges to the model; afferent blockade.**
318 Thus far our proposal has been based on correlative evidence, and observations
319 between studies. The strongest challenge to the idea that performance fatigability is
320 task-dependent and not regulated to a critical threshold is provided by experimental
321 studies that used an intrathecal opioid analgesic (fentanyl) to attenuate the activity of
322 group III/IV afferent feedback during exercise. These elegant studies have
323 consistently demonstrated that, when group III/IV afferent feedback is blocked by
324 fentanyl, participants voluntarily incur a higher degree of performance fatigability (8,
325 9, 32). The subsequent interpretation of these observations emphasize the decisive
326 role that group III/IV feedback from exercising skeletal muscle plays in determining
327 exercise tolerance, via sensory input that mediates central motor command during
328 exercise to constrain the development of performance fatigability to a specific,
329 unvarying, task-dependent level.
330
331 Although seemingly in opposition to our proposal, a reinterpretation of the data from
332 these studies provides support to the idea that the magnitude of performance
333 fatigability is dependent on the active muscle mass engaged, and disruption to
334 homeostasis in multiple physiological systems, which collectively combine to
335 modulate the symptom of fatigue and thus determine exercise tolerance. In addition to

attenuating the activity of group III/IV afferents, the administration of fentanyl also compromises the exercise pressor reflex, which results in an attenuation of the cardiopulmonary response to exercise (33). Consequently, the disruption to these physiological systems, and the demand for cardiac and respiratory muscle work, is attenuated, which theoretically reduces their input to modulating the symptom of fatigue (see Figure 4, Amann et al., 2009 (8), and Figure 3, Amann et al., 2011 (9)). We contend this enables the exerciser to recruit and exhaust a greater volume of the knee extensor musculature during the task for the same symptom of fatigue because there is less sensory input from, and/or demand on, the respiratory and cardiovascular systems, not because there is a compromised regulation to a critical threshold. In support of this proposal, the attenuated cardiovascular and respiratory response observed in these studies was concurrent with a greater recruitment of the knee extensor musculature during the cycling bout (see Figure 2, Amann et al., 2009 (8), and Figure 2, Amann et al., 2011, (9)) when group III/IV afferent feedback was blocked. Estimates of muscle activation via surface EMG are subject to a number of valid critiques (34-36), particularly a lack of sensitivity in detecting small differences in exercise intensity. Considering this, it is perhaps particularly striking that participants had a consistently higher surface EMG after fentanyl administration even though they were cycling at the same absolute intensity (9). Figure 2 illustrates this alternative reinterpretation; in panel A, the symptom of fatigue is modulated to a greater extent by adjustments in cardiovascular and respiratory systems, probably mediated primarily by the stress to cardiac and respiratory muscle. This sensory input indirectly limits the adjustments in contractile function by providing a greater contribution to the tolerable fatigue the exerciser is willing to endure. Panel B illustrates how these inputs change when group III/IV afferent feedback is blocked;

361 the relative input of cardiopulmonary adjustments to modulating fatigue is reduced,
362 which permits the exerciser to stress a greater degree of the locomotor skeletal muscle
363 before the maximum tolerable perception of fatigue is attained. These data also
364 demonstrate that, although skeletal muscle is the ultimate "limiter" of exercise
365 performance, disruption to other physiological systems can modulate the symptom of
366 fatigue even if such disruptions are submaximal relative to the higher capacity of
367 these systems (18).
368
369 **Does group III/IV afferent feedback from skeletal muscle contribute to fatigue?**
370 The activity of group III/IV afferent feedback from exercising skeletal muscle clearly
371 contributes to the optimal regulation of exercise by instigating adjustments in multiple
372 physiological systems in response to the homeostatic threat that exercise might
373 impose (33, 37). Without such feedback, exercise regulation is almost certainly
374 compromised, at least for high-intensity locomotor exercise lasting < 10 min (8, 9,
375 32). Indeed, Amann *et al*. (8, 9) clearly demonstrated that when such feedback is
376 blocked participants self-select exercise intensities and/or inappropriate recruitment
377 strategies that result in significant additional performance fatigability in comparison
378 to a control, with no improvement in exercise performance. These data clearly support
379 the idea that group III/IV afferent feedback is important for the regulation of exercise,
380 at least indirectly.
381
382 The critical threshold hypothesis proposes that metabolite-mediated, non-nociceptive
383 feedback also acts directly, in a negative feedback loop, on the central nervous system
384 to restrain central motor command to limit reductions in contractile function to a
385 specific level (7). In this review we have argued that adjustments in skeletal muscle as

a consequence of exhaustive exercise are intensity- and mode-dependent, and not regulated to a critical threshold. Additionally, it is questionable whether non-nociceptive group III/IV afferent feedback from skeletal muscle has any impact beyond the appropriate stimulation of the exercise pressor reflex. The potential modulating role of nociceptive (i.e. pain-related) discharge of group III/IV afferents on the recovery of muscle force and voluntary activation has been demonstrated using models of post-exercise circulatory occlusion (38-42), however whether non-nociceptive afferents act on the CNS is debatable (43-45). In this review we have conceptualized that disruptions to multiple physiological systems (including skeletal muscle) combine to modulate the symptom of fatigue via sensory "input", but the relative importance of such "inputs" is open to debate. Indeed, the neurophysiological basis of fatigue, and the extent to which afferent feedback determines endurance exercise performance remains the subject of fervent debate (44-48). Some theorists propose the fatigue experienced during exercise is mediated primarily by the integration of multiple afferent sensory inputs (49), whereas opponents cite the processing of corollary discharge from premotor/motor areas as the primary factor mediating the perception of effort experienced during exercise (50). A limitation within these debates is the concept of the RPE as a measure of fatigue is not described in detail to afford a valid comparison between studies (51). A detailed discussion is beyond the scope of the current review. Regardless of whether the fatigue experienced during exercise can be explained by afferent or efferent mechanisms, understanding the significance of different adjustments (both physiological and psychological) that contribute to fatigue, how these vary with the exercise task, and how the tolerance of fatigue can be modulated by intervention remain key questions for our understanding of human performance (2).

411

412 **CONCLUSION**

413 The critical threshold hypothesis proposes that group III/IV afferent feedback from
414 skeletal muscle acts directly on the central nervous system to restrain central motor
415 command and limit performance fatigability to a specific, unvarying level. Here we
416 propose the reduction in skeletal muscle contractile function observed after exercise is
417 task-dependent, and determined primarily by the active muscle mass engaged in the
418 exercise bout, the exercise intensity, and the associated disruption to whole body
419 homeostasis. When the active muscle mass is small, greater reductions in contractile
420 function specific to the exercising muscle can be tolerated before fatigue becomes
421 intolerable as the sensory input is confined to a small muscle mass, and disruptions to
422 other physiological systems are smaller. When the active muscle mass is increased,
423 the demands placed on a larger skeletal muscle mass, and the extra disruption to
424 homeostasis in the physiological systems that support exercise, combine and summate
425 to modulate the symptom of fatigue. Consequently, the tolerable level of fatigue the
426 exerciser is willing to endure is mediated less by adjustments in the involved skeletal
427 muscle, as other adjustments in whole body homeostasis contribute to the perception
428 of fatigue. For locomotor exercise the intensity of the task also modulates the
429 magnitude of performance fatigability, as higher exercise intensities will result in the
430 recruitment and subsequent stress of a greater volume of skeletal muscle. This
431 explains why performance fatigability is: i) exacerbated with greater exercise
432 intensity during locomotor exercise, ii) larger at termination of single-limb exercise
433 than double-limb exercise, and locomotor cycling compared with running exercise,
434 iii) is consistent between trials of the same exercise task, and iv) is altered in
435 conditions of “blocked” afferent feedback when the subsequent force or muscle

436 activation strategies are also altered. The hypothesis put forth in this review provides
437 a plausible alternative interpretation to the idea of a critical threshold, and further
438 experimental work to test this hypothesis is warranted.
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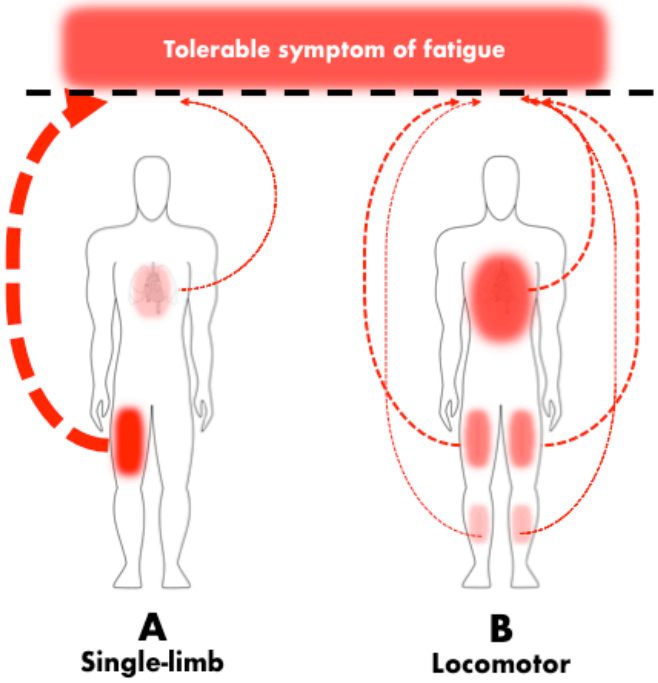
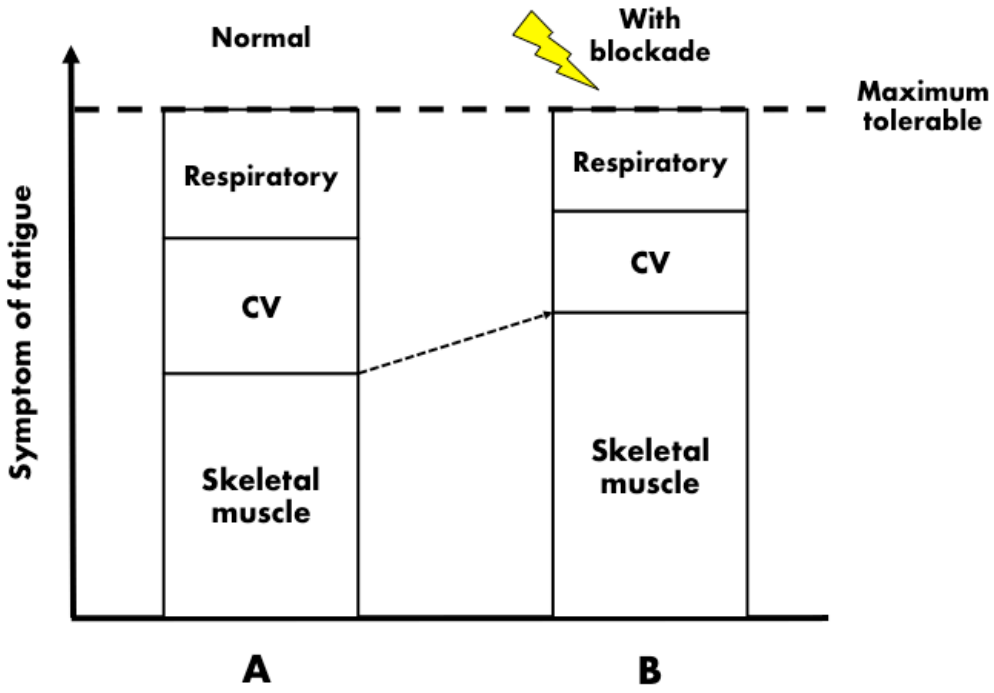
444 **List of Figures**



445

446 **Figure 1**. Simplified illustration of how the active muscle mass required of the
447 exercise task modulates the symptom of fatigue. In picture A, when a single muscle
448 group is exercised to the limit of tolerance, a strong, local disruption to the small
449 muscle mass involved in the task is the primary contributor to the symptom of fatigue
450 (represented by the thick arrow). In contrast, when the active muscle mass is
451 increased (picture B), the demands placed on i) a larger skeletal muscle mass (both
452 involved and non-involved), and ii) the disruption to homeostasis in other
453 physiological systems (cardiovascular, respiratory), all contribute to modulating the
454 symptom of fatigue (represented by a number of thin arrows). As a consequence, the
455 magnitude of performance fatigability, measured by reductions in the involuntary
456 potentiated twitch response to external stimulation, is reduced in the involved, active
457 musculature as other adjustments combine to modulate the symptom of fatigue.



458

459 **Figure 2**. Simplified schematic to demonstrate how potential modulators of the
460 symptom of fatigue are affected by afferent blockade. The compromised exercise
461 pressor response caused by administration of fentanyl precipitates a reduction in
462 cardiovascular (CV) and respiratory responses to exercise, and the subsequent work
463 of cardiac and respiratory muscle is reduced. The reduction in sensory input from
464 these systems allows the exerciser to incur greater reductions in skeletal muscle
465 contractile function before the maximum tolerable symptom of fatigue, which in
466 healthy individuals is strongly associated with the perception of effort, (represented
467 by the dashed line) is attained.

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